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Revascularization Strategies for Patients With Femoropopliteal Peripheral Artery Disease

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ABSTRACT

BACKGROUND No adequately powered studies exist to compare major clinical outcomes after endovascular therapy (EVT) with stent implantation vs bypass surgery (BSx) for symptomatic femoropopliteal peripheral artery disease.

OBJECTIVES This study sought to perform a pooled analysis of individual patient data from all randomized controlled trials comparing EVT vs BSx.

METHODS Principal investigators of 5 of 6 available randomized controlled trials agreed to pool individual patient data. The primary endpoint was major adverse limb events, a composite of all-cause death, major amputation, or target limb reintervention. Secondary endpoints included amputation-free survival, individual major adverse limb event components, and primary patency. Early complications were bleeding, infection, or all-cause death within 30 days.

RESULTS A total of 639 patients were analyzed with a mean age of 68.1 ± 9.1 years and 29.0% women. Baseline characteristics were comparable between groups. At 2 years, there were no significant differences between patients who received EVT and those who received BSx regarding major adverse limb events (40.1% vs 36.4%; log-rank $P = 0.447$; adjusted HR [aHR]: 1.04; 95% CI: 0.80-1.36), amputation-free survival (88.1% vs 90.0%; log-rank $P = 0.455$; aHR for death or amputation: 1.04; 95% CI: 0.63-1.71) and the other secondary endpoints except for primary patency, which was lower in patients who received EVT vs those who received BSx (51.2% vs 61.3%; log-rank $P = 0.024$; aHR for loss of primary patency: 1.31; 95% CI: 1.02-1.69). EVT was associated with significantly lower rates of early complications (6.8% vs 22.6%; $P < 0.001$) and shorter hospital stay (3.1 ± 4.2 days vs 7.4 ± 4.9 days; $P < 0.001$).

CONCLUSIONS These findings further support the efficacy and safety of EVT as an alternative to BSx in patients with symptomatic femoropopliteal peripheral artery disease. (J Am Coll Cardiol 2023;81:358–370) © 2023 by the American College of Cardiology Foundation.

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The prevalence of peripheral artery disease (PAD) is steadily increasing and affects more than 200 million patients worldwide.[1] Although the majority of patients with PAD are asymptomatic, many experience lifestyle-limiting claudication. Among these patients, a conservative approach with medical management to alleviate symptoms often fails and endovascular or surgical revascularization may eventually be indicated. In patients with critical limb ischemia (CLI), revascularization therapy reduces the risk of major limb events.[1] In the past, endovascular therapy (EVT) compared with surgical bypass (BSx) was associated with significantly lower rates of amputation-free survival.[2] These disadvantages were mainly attributed to the limited availability of endovascular devices to facilitate crossing occlusive lesions and prevent reocclusion after balloon angioplasty without stent implantation.[2] Since then, notable advancement in the EVT armamentarium and technique, including the introduction of stent implantation, has occurred.

More recent randomized controlled trials on EVT with stent implantation vs BSx found promising results for primary patency after EVT. However, no conclusions on clinical endpoints such as major adverse limb events (MALE) or amputation-free survival could be made because of the small sample sizes of the trials.[3-9] In light of the lack of robust evidence, we aimed to perform a pooled analysis of individual patient data from all randomized controlled trials comparing outcomes of patients with femoropopliteal PAD who are undergoing EVT with stent implantation vs BSx.

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METHODS

STUDY POPULATION. The aim of the REVIVE (Revascularization Strategies in Patients With Peripheral Arterial Disease Involving the Femoropopliteal Arteries) study was to pool individual patient data from all published randomized controlled trials investigating patients with intermittent claudication or CLI undergoing EVT with stent implantation (bare-metal, drug-eluting, or covered stent) vs BSx using either prosthetic or autologous vein grafts. We searched PubMed and EMBASE and websites such as ClinicalTrials.gov, tctMD, and LINC (Leipzig Interventional Course) for randomized clinical trials investigating patients with intermittent claudication or CLI caused by PAD involving the femoropopliteal arteries who were treated by EVT with stent implantation vs BSx. Citations were screened based on title and abstract by 3 independent reviewers (S.F., H.K., and P.K.). Potential eligible reports were retrieved and scrutinized for eligibility in full text. The reference list of available reports was reviewed for any eligible reports, which were not captured initially. Six trials were identified as meeting the eligibility criteria.[3-9] Principal investigators of all trials were invited to contribute to the study. Five principal investigators agreed to pool their data for this analysis. An Excel (Microsoft Corp) datasheet including baseline, procedural, post-procedural, and outcome data was provided to each principal investigator. After receiving datasheets of each included trial, data were investigated for consistency and completeness for harmonization, and merging of the data was performed. Supplemental Table 1 shows the key inclusion and exclusion criteria of each included study. All trials included in the present analysis complied with the provisions of the Declaration of Helsinki, and the Ethics Committees/Institutional Review Boards at the individual study centers approved the study protocols. All patients provided written informed consent for participation in the individual studies. The Institutional Review Board at the Icahn School of Medicine at

ABBREVIATIONS AND ACRONYMS

ABI = ankle-brachial index
BSx = surgical bypass
CLI = critical limb ischemia
EVT = endovascular therapy
MALE = major adverse limb events
PAD = peripheral artery disease

TABLE 1 Baseline Clinical Characteristics

	Overall (N = 639)	EVT (n = 325)	BSx (n = 314)	*P* Value
Age, y	68.3 ± 9.1	68.9 ± 9.3	67.7 ± 8.8	0.088
Female	185 (29.0)	104 (32.0)	81 (25.8)	0.084
BMI, kg/m^2	26.7 ± 4.6	26.6 ± 4.8	26.8 ± 4.4	0.831
Current smoker	267 (42.1)	132 (40.6)	135 (43.7)	0.433
Hypertension	485 (76.0)	237 (73.1)	248 (79.0)	0.085
Hyperlipidemia	404 (63.3)	197 (60.8)	207 (65.9)	0.180
Diabetes mellitus	210 (32.9)	106 (32.6)	104 (33.1)	0.892
Chronic kidney disease	136 (22.8)	64 (21.3)	72 (24.3)	0.372
Coronary arterial disease	158 (30.8)	84 (32.2)	74 (29.4)	0.489
Cerebrovascular disease	47 (9.1)	26 (9.9)	21 (8.3)	0.532
Prior peripheral arterial disease	207 (40.3)	82 (31.3)	125 (49.6)	<0.001
Ankle brachial index	0.56 ± 0.15	0.58 ± 0.15	0.54 ± 0.14	0.002
Rutherford classification				0.974
Mild	7 (1.1)	4 (1.2)	3 (1.0)	
Moderate	34 (5.3)	17 (5.2)	17 (5.4)	
Severe	350 (54.8)	183 (56.3)	167 (53.2)	
Rest pain	100 (15.6)	49 (15.1)	51 (16.2)	
Mild tissue loss	144 (22.5)	70 (21.5)	74 (23.6)	
Major tissue loss	4 (0.6)	2 (0.6)	2 (0.6)	
Presentation				0.361
Intermittent claudication	392 (61.3)	205 (63.1)	187 (59.6)	
Critical limb ischemia or acute limb ischemia	247 (38.7)	120 (36.9)	127 (40.4)	

Values are mean ± SD or n (%).
BMI = body mass index; BSx = bypass surgery; EVT = endovascular therapy.

TABLE 2 Baseline Procedural Characteristics and Medication at Discharge

	Overall (N = 639)	EVT (n = 325)	BSx (n = 314)	*P* Value
Type of stent				
BMS	103 (31.7)	103 (31.7)	0 (0.0)	
Covered stent	86 (26.5)	86 (26.5)	0 (0.0)	
DES	136 (41.8)	136 (41.8)	0 (0.0)	
Type of surgery				
Synthetic	166 (52.9)	0 (0.0)	166 (52.9)	
Autologous vein	148 (47.1)	0 (0.0)	148 (47.1)	
TASC classification				0.191
B	45 (7.1)	28 (8.7)	17 (5.5)	
C	152 (24.1)	81 (25.2)	71 (22.9)	
D	435 (68.8)	213 (66.1)	222 (71.6)	
Chronic total occlusion	562 (88.6)	277 (86.0)	285 (91.3)	0.035
Lesion length, cm	23.6 ± 8.2	23.0 ± 8.1	24.2 ± 8.3	0.071
Angiographic runoff, no. of vessels				0.340
0	6 (1.5)	3 (1.5)	3 (1.6)	
1	76 (19.3)	46 (22.7)	30 (15.7)	
2	156 (39.6)	75 (36.9)	81 (42.4)	
3	156 (39.6)	79 (38.9)	77 (40.3)	
Concomitant CFA treatment	74 (11.6)	24 (7.4)	50 (15.9)	<0.001
Technical failure	23 (3.6)	23 (7.1)	0 (0.0)	<0.001
Medications at discharge				
Anticoagulants	102 (24.4)	41 (19.4)	61 (29.5)	0.017
Aspirin	335 (80.7)	169 (80.9)	166 (80.6)	0.943
$P2Y_{12}$ inhibitor	225 (54.3)	170 (81.3)	55 (26.8)	<0.001
Lipid lowering therapy	276 (74.4)	138 (74.2)	138 (74.6)	0.929
Insulin use	22 (10.5)	8 (7.8)	14 (13.2)	0.200

Values are n (%) or mean ± SD.

BMS = bare-metal stent; CFA = common femoral artery; DES = drug-eluting stent; TASC = Trans-Atlantic Inter-Society Consensus; other abbreviations as in Table 1.

Mount Sinai approved the pooling and analysis of the patient-level data. This individual patient data analysis has been registered in the PROSPERO public database (CRD42021275749).

ENDPOINTS. The primary endpoint of this analysis was MALE, a composite of all-cause death, major amputation, or reintervention of target limb (either target vessel or target lesion revascularization as per individual trial protocol). Secondary endpoints included amputation-free survival, all-cause death, major amputation, reintervention of the target limb, and primary patency as per individual trial definition. Postprocedural clinical status and change over time were evaluated by assessing ankle-brachial index (ABI) and determination of Rutherford class. The safety endpoint was early complications, defined as 30-day complication rate, and a composite of any bleeding, infection, or all-cause death. The latter definition was chosen as these data were available in each of the included trials. Two patients were lost to follow-up with regard to the 30-day safety endpoint. Lastly, the length of hospitalization was collected.

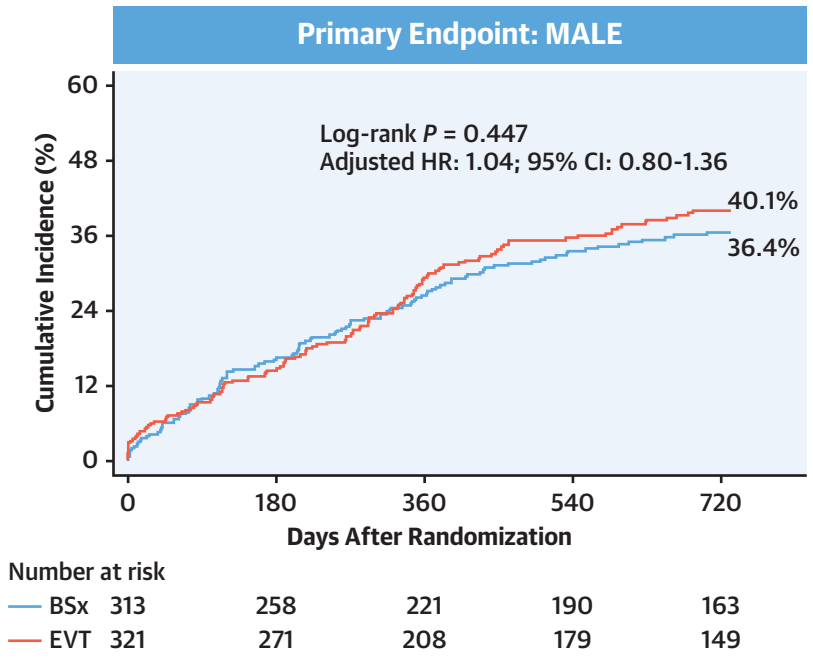
STATISTICAL ANALYSIS. Descriptive statistics were computed to compare baseline clinical features, procedural characteristics, and postprocedural complications up to 30 days between EVT and BSx groups. Continuous variables were summarized as mean ± SD, and categorical variables were presented as frequencies (proportion), with the Student's *t*-test and chi-square test used to test differences. Mann-Whitney *U* test and Fisher exact test were applied when the test assumptions were not met. The cumulative incidences of the outcomes of interest were estimated using the Kaplan-Meier method. Patients not experiencing an endpoint within 2 years from randomization were censored at the last known contact or at 732 days, whichever came first. To account for the between-study heterogeneity after pooling the data from 5 centers, we fitted the Cox proportional-hazards models with a cluster-specific random effect term to examine the 2-year outcomes comparing EVT with BSx. Adjusted HRs (aHR) and their 95% CIs were obtained after we controlled for the covariates that were found imbalanced at baseline, including lesion type and concomitant common femoral artery treatment. In this study, 23 subjects had technical failure after being randomized to the EVT group. Sensitivity analysis was conducted in the population without these 23 subjects. No issue with individual participant data integrity could be detected.

Data management was performed using Stata (version 16.0, Stata Corp). All statistical analyses were performed using SAS (version 9.4, SAS Institute, Inc). Two-tailed $P < 0.05$ was considered statistically significant.

RESULTS

BASELINE CHARACTERISTICS. The median follow-up duration was 2.12 years (IQR: 1.84-2.45 years). A PRISMA individual participant data flow diagram is presented in Supplemental Figure 1. Of the 639 patients enrolled in 5 randomized controlled trials, 325 (50.9%) were assigned to EVT and 314 (49.1%) were assigned to BSx. Table 1 depicts the baseline clinical characteristics. The mean age was 68.3 ± 9.1 years, and 29.0% of patients (n = 185) were women. The overall rates of intermittent claudication and CLI were 61.3% and 38.7%, respectively. There were no differences in baseline clinical characteristics between patients assigned to EVT vs those assigned to BSx with the exception of baseline ABI, which was significantly higher in the EVT than the BSx group (0.58 ± 0.15 vs 0.54 ± 0.14; $P = 0.002$). There were no significant differences in the distribution of

FIGURE 1 Primary Endpoint Comparing EVT With BSx



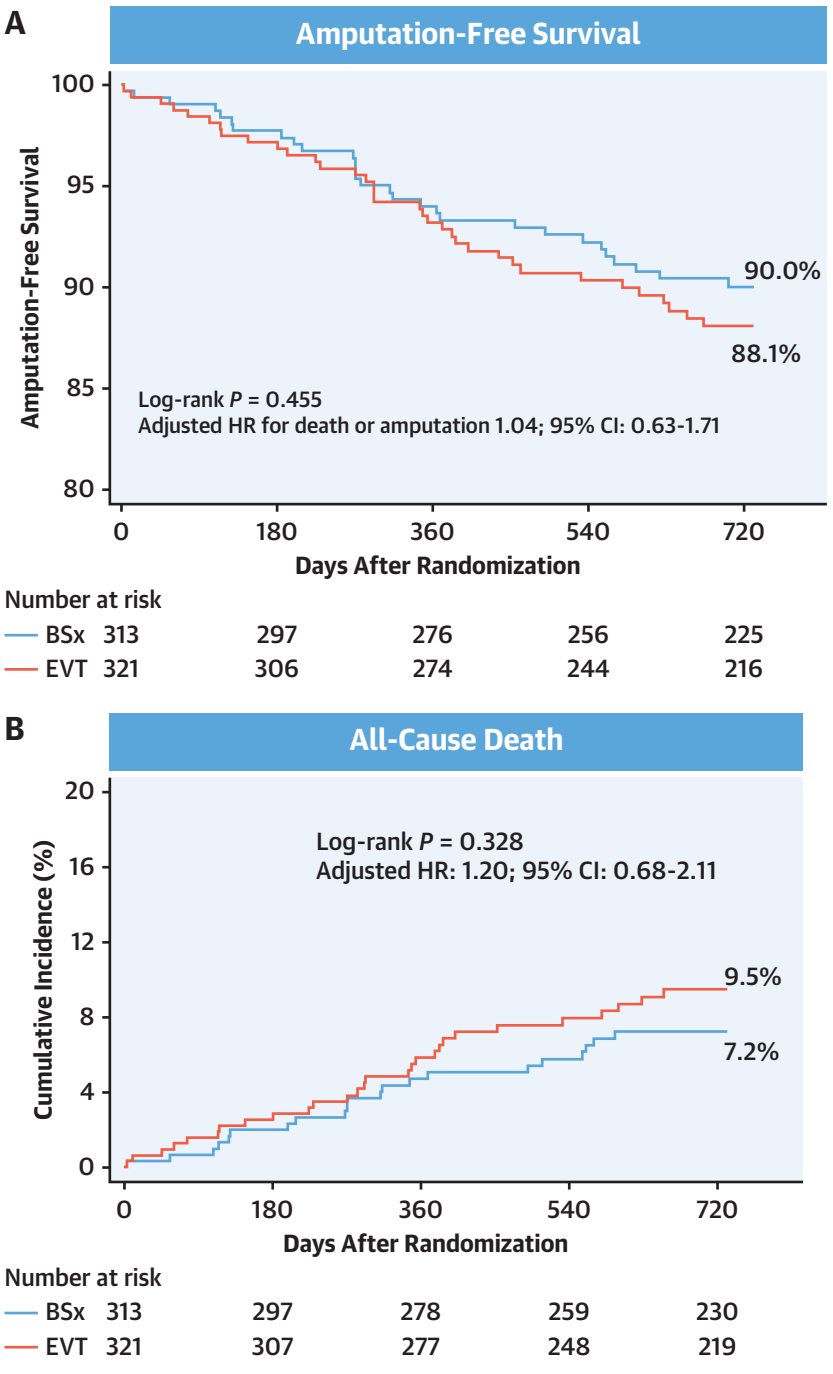
Cumulative rates of the primary endpoint of major adverse limb events (MALE) during 2 years of follow-up. BSx = bypass surgery; EVT = endovascular therapy.

Rutherford classification and presentation with intermittent claudication vs CLI between the treatment groups. Table 2 depicts the procedural characteristics and medication at discharge. Patients assigned to EVT underwent bare-metal stent, covered stent, and drug-eluting stent implantation in 31.7%, 26.5%, and 41.8%, respectively, whereas patients assigned to BSx received synthetic (polytetrafluoroethylene or Dacron) and autologous vein grafts in 52.9% and 47.1%. There were no differences with respect to disease severity, based on TASC (TransAtlantic Inter-Society Consensus) II criteria, between groups. Although the individual studies did not have significant differences in the rates of chronic total occlusion (Supplemental Figure 2), the patient-level pooled data showed significantly lower rates in patients assigned to EVT than in those assigned to BSx (86.0% vs 91.3%; $P = 0.035$). Concomitant treatment of the common femoral artery was significantly lower in the EVT group vs the BSx group (7.4% vs 15.9%; $P < 0.001$). Technical failure occurred only in the EVT but not in the BSx group (7.1% vs 0%; $P < 0.001$). Discharge on clopidogrel was more frequent in patients in the EVT group, and discharge on anticoagulants was more frequent in those in the BSx group. There were no differences between the EVT and BSx groups in aspirin, lipid-lowering, and insulin use at discharge.

PRIMARY AND SECONDARY OUTCOMES. After 2 years of follow-up, there was no significant difference in the incidence of MALE between the EVT and BSx groups (40.1% vs 36.4%; $P = 0.447$; aHR: 1.04; 95% CI: 0.80-1.36) (Figure 1). Similarly, there were no significant differences in amputation-free survival, all-cause death, major amputation, and reintervention of the target limb (Figures 2A to 2D). Regarding primary patency, patients from the EVT group had a significantly lower rate than patients in the BSx group did (51.2% vs 61.3%; $P = 0.024$; aHR for loss of primary patency: 1.31; 95% CI: 1.02-1.69). After exclusion of patients with technical failure of the index procedure, primary patency remained lower in EVT compared with in BSx, but the difference did not reach statistical significance anymore (53.6% vs 61.3%; $P = 0.140$; aHR for loss of primary patency: 1.19; 95% CI: 0.92-1.54).

SUBGROUP ANALYSES. Treatment effects with respect to the primary endpoint were similar across the subgroups of age (≤75 vs >75 years), sex,

FIGURE 2 Secondary Endpoints Comparing EVT With BSx



(A) Amputation-free survival over 2 years of follow-up. **(B)** Cumulative rates of all-cause death during 2 years of follow-up. **(C)** Cumulative rates of major amputation during 2 years of follow-up. **(D)** Cumulative rates of reintervention of target limb during 2 years of follow-up. Abbreviations as in Figure 1.

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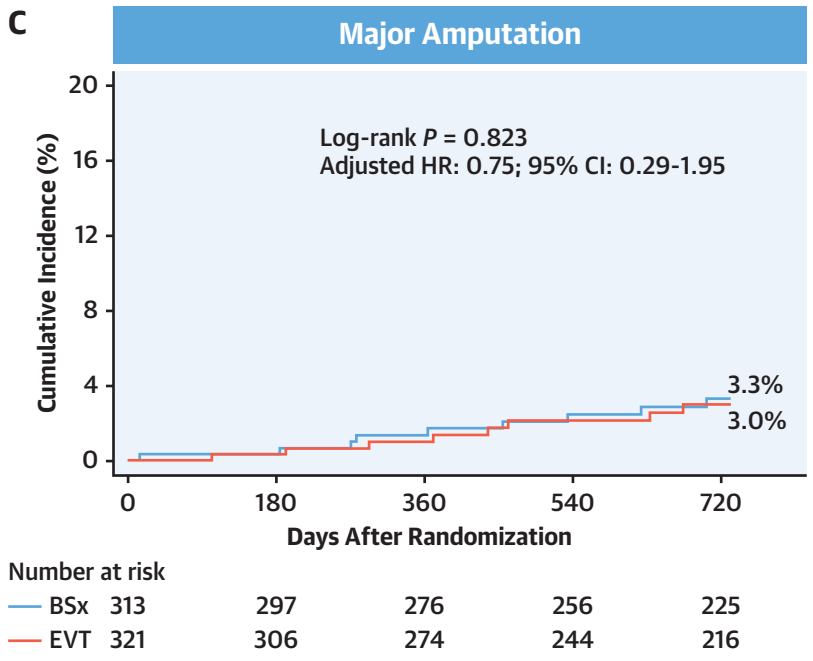
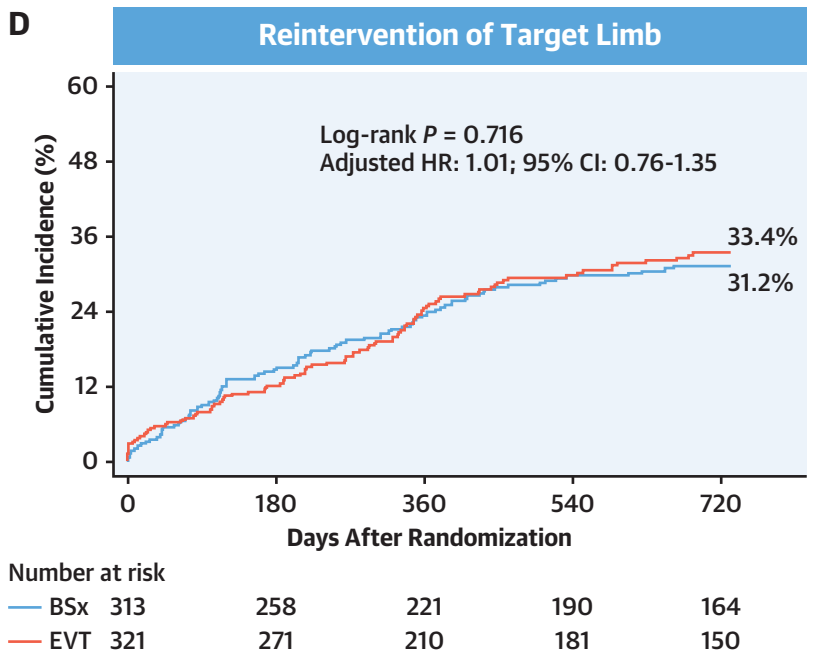
FIGURE 2 Continued



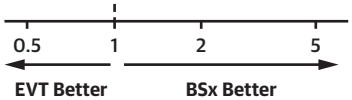


diabetes, clinical presentation (intermittent claudication vs CLI), lesion type (stenotic vs occlusive), lesion length (≤20 vs >20 cm), and concomitant common femoral artery treatment (Figure 3). There was a significant interaction between treatment assignment and TASC II classification, with significantly better outcome associated with BSx vs EVT in TASC II B or C but not in TASC II D lesions ($P_{interaction}$ = 0.033) (Figure 3).

POSTPROCEDURAL CLINICAL STATUS AND CHANGE OVER TIME. Table 3 depicts the postprocedural clinical status and change over time by treatment group. Overall, postprocedural ABI was significantly

FIGURE 3 Primary Endpoint Comparing EVT With BSx Within Subgroups

	No. of pts	EVT n Events (%)	BSx n Events (%)	HR (95% CI)	Interaction *P* Value
Age					
≤75 y	481	83 (38.2)	89 (37.7)	1.00 (0.74-1.35)	0.195
>75 y	158	38 (44.8)	21 (32.0)	1.50 (0.88-2.56)	
Sex					
Male	454	80 (39.7)	77 (34.4)	1.13 (0.83-1.55)	0.725
Female	185	41 (40.6)	33 (42.1)	1.01 (0.64-1.60)	
Diabetes mellitus					
No	429	74 (35.9)	76 (37.7)	0.91 (0.66-1.25)	0.053
Yes	210	47 (48.8)	34 (34.0)	1.62 (1.04-2.53)	
Presentation					
Intermittent claudication	392	71 (37.7)	61 (34.5)	1.09 (0.77-1.53)	0.826
Critical/acute limb ischemia	247	50 (44.0)	49 (39.1)	1.15 (0.77-1.70)	
TASC classification					
B/C	197	42 (43.2)	22 (25.7)	1.81 (1.08-3.04)	0.033
D	435	78 (38.7)	86 (40.2)	0.94 (0.69-1.28)	
Lesion type					
Stenotic	72	23 (55.2)	10 (37.0)	1.63 (0.78-3.44)	0.258
Occlusive	562	97 (37.7)	99 (36.2)	1.03 (0.78-1.37)	
Lesion length					
≤20 cm	224	43 (38.7)	32 (33.1)	1.15(0.73-1.82)	0.887
>20 cm	407	77 (41.3)	77 (38.0)	1.10(0.80-1.51)	
Concomitant CFA treatment					
No	565	113 (40.5)	101 (40.0)	0.99 (0.76-1.30)	0.136
Yes	74	8 (34.9)	9(18.4)	2.07 (0.80-5.37)	



Forest plot for the primary endpoint of major adverse limb events within key subgroups. CFA = common femoral artery; TASC = Trans-Atlantic Inter-Society Consensus; other abbreviations as in Figure 1.

lower in patients in the EVT group than in those in the BSx group (0.86 ± 0.20 and 0.92 ± 0.17, respectively; $P < 0.001$). Similarly, EVT compared with BSx was associated with significantly less ABI improvement between baseline and postprocedure (0.28 ± 0.22 vs 0.39 ± 0.19, respectively; $P < 0.001$). There was no difference in the Rutherford classification at 6, 12, and 24 months between EVT and BSx. Although the improvement in Rutherford class was significantly less in patients in the EVT group than in those in the BSx group between baseline and 6 months (85.7% vs 92.0%; $P = 0.019$), there was no significant difference in improvement of Rutherford class between baseline and 12 months (91.1% vs 91.5%; $P = 0.855$) and baseline and 24 months (85.9% vs 91.6%; $P = 0.055$).

SAFETY ENDPOINT AND LENGTH OF HOSPITALIZATION. The composite endpoint of early complications and its individual components by treatment groups are depicted in Figure 4. EVT, compared with BSx, was associated with a significantly lower rate of the composite of any bleeding, infection, or all-cause death within 30 days (6.8% vs 22.6%; $P < 0.001$) driven by the occurrences of any bleeding (4.9% vs 9.9%; $P = 0.017$) and infection (1.5% vs 15.3%; $P < 0.001$) with no significant difference in death (0.6% vs 0.3%; $P = 1.000$). Hospitalization was significantly shorter in patients in the EVT group than in those in the BSx group (3.1 ± 4.2 days vs 7.4 ± 4.9 days; $P < 0.001$).

DISCUSSION

The key findings of the present pooled analysis of individual patient data investigating the efficacy and safety of EVT with stent implantation as compared to

BSx using prosthetic or autologous vein grafts at 2 years are the following (**Central Illustration**). First, there were no significant differences in the incidence of MALE, amputation-free survival, and the other secondary endpoints except for a lower rate of primary patency in EVT compared with in BSx. Second, there was no difference between EVT and BSx in the primary endpoint of MALE within key subgroups except for a significantly lower risk of MALE associated with BSx than with EVT in TASC II B or C but not in TASC II D lesions with significant interaction between treatment strategy and TASC II classification. Third, although EVT vs BSx resulted in less improvement of ABI and Rutherford class from before to early after the procedure, Rutherford class improvement was documented in approximately 90% of all patients with no significant differences between treatment groups at 12 and 24 months. Fourth, EVT was associated with significantly lower rates of early complications and shorter hospitalization than BSx was.

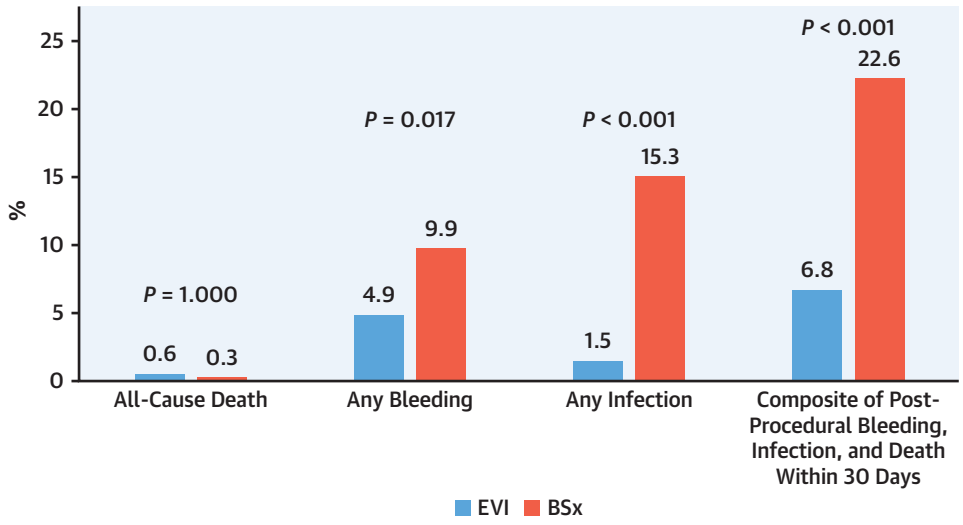
Revascularization for femoropopliteal artery PAD aims to improve quality of life and functional capacity after failure of conservative approaches in patients with intermittent claudication and limb salvage and survival in patients with CLI.[10-12] PAD in this segment is highly prevalent. At the same time, the femoropopliteal artery is subject to several external forces, including torsion, flexion, extension, and compression, making it challenging to treat. Whereas in the past, BSx has been regarded as the standard of care[13] and remains indicated especially in patients with complex disease,[10-12,14] notable advancements in the EVT armamentarium and technique, including the introduction of stent implantation over the past decades, have resulted in promising evidence suggesting similar primary patency rates in EVT vs BSx.[5,7,9,15] With respect to clinical endpoints, the BASIL (Bypass Versus Angioplasty in Severe Ischemia of the Leg) trial[2] was the only large-scale, randomized controlled trial powered to investigate amputation-free survival after EVT vs BSx in patients with severe limb ischemia involving the femoropopliteal segment. At 2 years, no significant difference in amputation-free survival between treatment strategies was found, although a post hoc analysis showed diverging curves in favor of BSx beyond 2 years.[2] It is important to note that this trial completed enrollment in 2004, and plain balloon angioplasty without stent implantation was used in the EVT group. A meta-analysis published in 2013, including 4 randomized controlled trials and 6 observational studies of patients with femoropopliteal artery PAD, found lower primary patency in patients in the EVT group vs those in the BSx group at 1, 2, and 3 years. In addition, lower amputation-free and overall survival rates were found in the BSx group.[16] The inclusion of observational studies and studies not using a strategy with stent implantation limit the applicability of these findings to contemporary endovascular practice. The investigators concluded that high-level evidence demonstrating the superiority of one method over the other is lacking.[16] Since the publication of this meta-analysis, 4 additional randomized controlled trials using a strategy with stent implantation have been performed.[5-9] These studies found similar primary

TABLE 3 Postprocedural Clinical Status

	Overall (N = 639)	EVT (n = 325)	BSx (n = 314)	*P* Value
Postprocedural ABI	0.89 ± 0.19	0.86 ± 0.20	0.92 ± 0.17	<0.001
Change in ABI	0.34 ± 0.21	0.28 ± 0.22	0.39 ± 0.19	<0.001
Rutherford classification at 6 mo				0.905
None	208 (73.5)	103 (72.5)	105 (74.5)	
Mild	32 (11.3)	17 (12.0)	15 (10.6)	
Moderate	21 (7.4)	10 (7.0)	11 (7.8)	
Severe	11 (3.9)	7 (4.9)	4 (2.8)	
Rest pain	4 (1.4)	2 (1.4)	2 (1.4)	
Mild tissue loss	6 (2.1)	2 (1.4)	4 (2.8)	
Major tissue loss	1 (0.4)	1 (0.7)	0 (0.0)	
Rutherford classification improved at 6 mo	493 (88.8)	240 (85.7)	253 (92.0)	0.019
Rutherford classification at 12 mo				0.430
None	194 (69.8)	92 (66.2)	102 (73.4)	
Mild	37 (13.3)	24 (17.3)	13 (9.4)	
Moderate	24 (8.6)	13 (9.4)	11 (7.9)	
Severe	14 (5.0)	6 (4.3)	8 (5.8)	
Rest pain	3 (1.1)	1 (0.7)	2 (1.4)	
Mild tissue loss	5 (1.8)	2 (1.4)	3 (2.2)	
Major tissue loss	1 (0.4)	1 (0.7)	0 (0.0)	
Rutherford classification improved at 12 mo	473 (91.3)	235 (91.1)	238 (91.5)	0.855
Rutherford classification at 24 mo				0.164
None	168 (68.9)	69 (61.1)	99 (75.6)	
Mild	30 (12.3)	18 (15.9)	12 (9.2)	
Moderate	24 (9.8)	12 (10.6)	12 (9.2)	
Severe	16 (6.6)	10 (8.8)	6 (4.6)	
Rest pain	2 (0.8)	1 (0.9)	1 (0.8)	
Mild tissue loss	4 (1.6)	3 (2.7)	1 (0.8)	
Rutherford classification improved at 24 mo	406 (88.8)	189 (85.9)	217 (91.6)	0.055
Minimum Rutherford classification				0.292
None	281 (86.7)	136 (83.4)	145 (90.1)	
Mild	25 (7.7)	17 (10.4)	8 (5.0)	
Moderate	9 (2.8)	4 (2.5)	5 (3.1)	
Severe	5 (1.5)	4 (2.5)	1 (0.6)	
Rest pain	2 (0.6)	1 (0.6)	1 (0.6)	
Mild tissue loss	2 (0.6)	1 (0.6)	1 (0.6)	
Rutherford classification ever improved	566 (94.5)	285 (94.1)	281 (94.9)	0.640

Values are mean ± SD or n (%).
ABI = ankle-brachial index; other abbreviations as in **Table 1**.

FIGURE 4 Early Complications Within 30 Days After the Assigned Treatment



BSx = bypass surgery; EVI = endovascular intervention.

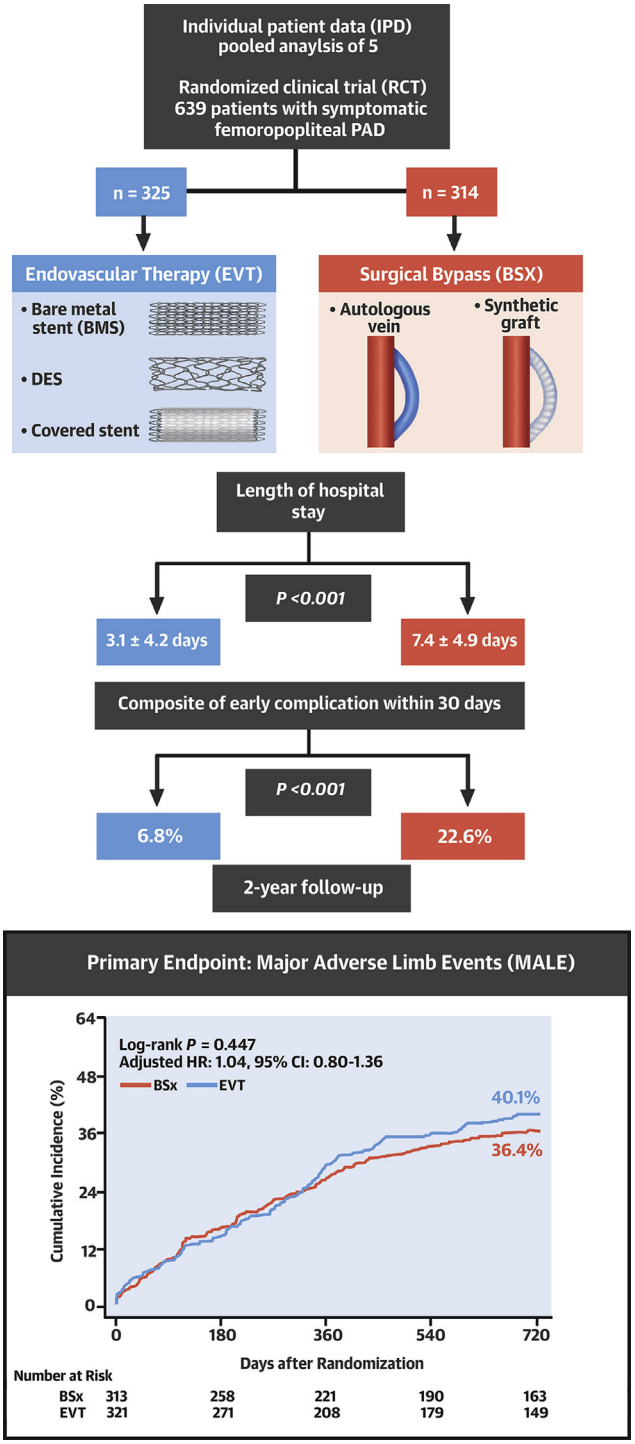
patency rates after EVT vs BSx.[5,6,8,9] However, because of the small sample sizes, no conclusive statement could be derived regarding MALE or amputation-free survival.

In the current analysis, we pooled individual patient data from all randomized controlled trials comparing EVT using stent implantation with BSx in patients with femoropopliteal PAD and found no significant differences in MALE and amputation-free survival between treatment strategies. Whereas the individual randomized controlled trials were too small to derive definitive conclusions on the effect of the different treatment strategies on these clinical endpoints, observational studies with larger sample sizes have shown mixed results.[17,18-23] To date, this analysis is the most robust evidence on the comparison of EVT with stent implantation vs BSx for these clinical endpoints.

Findings on the primary endpoint were reproducible in all subgroups except for a significant interaction between treatment strategy and TASC II classification resulting from a lower risk of MALE associated with BSx in patients with TASC II B or C but not TASC II D lesions. This particular finding is surprising and is not in keeping with previous evidence and guideline recommendations to treat more complex lesions with BSx and less complex lesions with EVT.[10,12,15,17,18,24] The explanation for these results must remain uncertain but may be attributed to the definition of TASC IIC lesions, which was the majority of this group. TASC IIC lesions are defined as multiple stenoses/occlusions totaling more than 15 cm or failed prior EVT, which may be managed better with BSx than EVT. One should also take into account the possibility of chance considering the small sample size of this subgroup analysis. Similarly, the group of patients with concomitant common femoral artery treatment was small and did not show a difference in outcome with EVT vs BSx. Of note, the majority of patients who received common femoral artery treatment had endarterectomy (70 of 74) regardless of the assigned treatment, whereas the remaining 4 patients were treated by endovascular approach (data not shown in the manuscript).

Interestingly, despite similar outcomes in MALE and amputation-free survival, primary patency in our analysis was significantly lower with EVT than BSx. In this regard, it is important to notice that there were 23 patients (7.1%) in the EVT group and 0 patients in the BSx group with technical failure of the index procedure. The majority of the technical failures were caused by the inability to cross the lesion and deliver the stent.[5,6,8,9] Because we assumed that these patients could have driven the difference in primary patency between treatment groups, we performed additional analyses excluding these patients and found that the difference was not significant anymore. Data from observational studies indicate a higher rate of technical success with the use of alternative access such as distal superficial femoral

CENTRAL ILLUSTRATION **Outcomes of Symptomatic Peripheral Artery Disease Patients Involving the Femoropopliteal Arteries**



Farhan S, et al. J Am Coll Cardiol. 2023;81(4):358–370.

BSx = bypass surgery; DES = drug-eluting stent; EVT = endovascular therapy; MALE = major adverse limb events; PAD = peripheral artery disease.

artery or tibiopedal access.[25-27] However, these approaches were only used in 24 cases of 1 trial[9] included in this analysis.

Regarding clinical status, compared with BSx, EVT resulted in less improvement of ABI and Rutherford class from before to early (6 months) after the procedure. However, improvement of Rutherford class was documented in approximately 90% of all patients regardless of assigned treatment strategy at 12 and 24 months. The reasons for the apparently slower improvement of functional status after EVT vs BSx early on are uncertain. However, interpretations regarding functional status based on Rutherford classification should take into account their limitations. The distinctions of some Rutherford classes are rather arbitrary and highly subjective. More objective measures for functional status, such as the Short Form 36 Health Status questionnaire and walking impairment questionnaire, were not routinely collected in all studies of our pooled analysis. Earlier studies have suggested that change in clinical status has an impact on MALE; however, these were observational studies with limited ability to derive definitive conclusions.[28]

In keeping with previous findings,[16,21,29] the risk of early complications driven by infection and bleeding was significantly lower, and hospitalization was significantly shorter in patients undergoing EVT vs those undergoing BSX.

Two ongoing trials[30,31] will provide more evidence on EVT vs BSx with respect to MALE, amputation-free survival, and primary patency in femoropopliteal artery PAD. More robust data on patients with CLI are awaited from the BEST-CLI (Best Endovascular Versus Best Surgical Therapy for Patients With Critical Limb Ischemia) study,[30] a pragmatic large-scale randomized controlled trial comparing best EVT including drug-coated balloon or stents vs BSx with synthetic or autologous veins. Until these studies are completed and results published, our analysis will remain the most robust evidence on treatment strategies in patients with femoropopliteal artery PAD.

STUDY LIMITATIONS. The included trials were conducted over 2 decades, with the earliest study initiated in 2003 and the last being published in 2022. Over this period, EVT has undergone tremendous advancement in technique and device technology. For instance, covered stents underwent several iterations and modifications over this time with marked improvement (eg, in radial strength and deliverability) in newer vs earlier generations.[32] These developments partially contributed to a certain heterogeneity of treatment strategies in the EVT group (eg, use of bare-metal, drug-eluting, and covered stents) and in the BSx group (eg, use of Dacron, polytetrafluoroethylene, and vein graft). Furthermore, the inclusion and exclusion criteria of individual trials differed slightly. Such differences were accounted for by adjusting outcomes for differences for these factors. However, residual or unmeasured confounding cannot be excluded. In addition, there was variability in endpoint definitions in the pooled individual studies. Also, stent fractures were not systematically collected in the present and therefore the impact of stent fractures on outcomes of patients assigned to EVT cannot be evaluated. Another important consideration refers to the fact that all patients included in the analysis were deemed eligible for either EVT or BSx. Therefore, our finding may not be applicable to patients in whom one approach is deemed more appropriate over the other.[10,12] Finally, we report discharge medication, including lipid-lowering therapy, antithrombotic treatment, and insulin but information on the rate of patients on guideline-directed medical therapy, including antihypertensive therapy, was not collected in the individual trials. In addition, guideline-directed medical therapy has changed over the past 2 decades.

CONCLUSIONS

In patients with symptomatic PAD involving the femoropopliteal segment, EVT with stent implantation compared with BSx was associated with similar 2-year rates of MALE and amputation-free survival but lower rates of early complications and shorter length of hospitalization. This pooled analysis of individual patient data further supports the efficacy and safety of EVT with stent implantation as an alternative to BSx in this patient population.

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Medical, Stel, and CONTROLRAD (spouse); has served on Scientific Advisory Boards for AMA, ACC (BOT Member), and SCAI (Women in Innovations Committee Member); has served as a, *JAMA* Associate Editor; and has served on the faculty of the Cardiovascular Research Foundation (no fee). Dr Reijnen has received consulting fees from WL Gore. Dr Krishnan has received consulting fees from Medtronic Vascular, Abbott Vascular, and Phillips. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: For patients with PAD involving the femoropopliteal segment, EVT with stent implantation is associated with 2 year rates of MALE and amputation-free survival that are similar to those for BSx but a lower incidence of early complications and shorter hospitalization.

TRANSLATIONAL OUTLOOK: The results of ongoing clinical trials should better inform the selection of an endovascular vs surgical approach for patients with femoropopliteal artery disease who are in need of revascularization.

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KEY WORDS bypass surgery, endovascular therapy, infrainguinal arteries, peripheral artery disease, stent

APPENDIX For supplemental figures and a table, please see the online version of this paper.